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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/473,830	12/28/99	LEIDEN J	2844/53802

HM22/0801

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EXAMINER	
CONNELL, Y	
ART UNIT	**PAPER NUMBER**
1633	4

DATE MAILED: 08/01/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/473,830	Leiden et al.
Examiner	**Group Art Unit**
Yvette Connell Albert	1633

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-23 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-23 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of transducing explanted and perfused hearts of C57BL/6 mice with 1.5 X 10.9 IU of AAV/CMV-lacZ for 15 minutes via a catheter in the left common carotid artery, does not reasonably provide enablement for a method of treating any cardiovascular condition by infusing rAAV into any coronary artery or any coronary sinus for any period of time in any amount sufficient to stably and efficiently transduce cardiomyocytes perfused by said artery or said sinus, wherein said AAV vector encodes at least one nucleic acid operably linked to any control region, said nucleic acid encoding any therapeutically effective molecule and expressing said therapeutic molecule in an amount effective to ameliorate said cardiovascular condition in any mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

1. Claimed invention. The claims are directed to a method of treating a cardiovascular condition by infusing a rAAV vector into a coronary artery or sinus for a time and in an amount

sufficient to stably and efficiently transduce cardiomyocytes perfused by said artery or said sinus, wherein said AAV vector encodes at least one nucleic acid operably linked to a control region, said nucleic acid encoding a therapeutically effective molecule and expressing said therapeutically effective molecule in an amount effective to treat or ameliorate said cardiovascular condition. The claims are also drawn to a method of treating a cardiovascular condition wherein the AAV transduces about 10% of cardiomyocytes; wherein the AAV is infused for at least 2 minutes; wherein the amount of AAV is about 1.5 x 10.5 IU AAV per gram body weight; wherein the therapeutically effective molecule is an antisense RNA or protein; wherein the cardiovascular condition is restenosis, arthersclerosis, congestive heart failure, ischemic cardiomyopathy, malignant arrhythmia, myocardial infarction, or dilated and hypertrophic cardiomyopathy.

2. The *in vitro* and *in vivo* examples and results on pages 10-12 shows that applicant was successful in preparing and purifying rAAV. Applicant was also successful in demonstrating the results obtained when adult C57BL/6 mice hearts were perfused with AAV/CMV-lacZ , after which hearts were transplanted into the necks of syngeneic hosts, and the arterial circulation reestablished by anastomosis of the transplanted aorta to the recipient carotid artery. The transplanted and revascularized hearts resumed beating until recipient mice were sacrificed 2, 4, or 8 weeks post transplantation and cardiac homogenates assayed for beta galactosidase activity. The results suggest that 4 weeks after perfusion about 40% of cardiomyocytes were beta-gal positive, a number which increased to greater than 50% several weeks post transplantation.

Therefore, rAAV delivered by coronary artery perfusion could be used to stably transduce cardiomyocytes throughout the myocardium.

3. It is not readily apparent that one skilled in the art given applicant's disclosure alone, would be able to practice the invention over the scope as claimed in view of the lack of guidance provided in the specification as filed and the known unpredictability in the art. In the instant specification, the claims embrace a method of treating any cardiovascular condition by infusing a rAAV vector into any coronary artery or sinus in an amount to stably and efficiently transduce cardiomyocytes perfused by said artery or sinus, wherein said AAV vector encodes at least one nucleic acid operably linked to a control region encoding any therapeutically effective molecule which when expressed would treat or ameliorate any cardiovascular condition. It is unclear that the state of the art regarding cardiovascular gene therapy at the time of filing was such that one skilled in the art would have been able to routinely treat or ameliorate any cardiovascular condition in any mammalian species, as broadly claimed. Such is considered to require undue experimentation.

It is also not readily apparent how the expression of lacZ gene is correlative of, or broadly enables the expression of any therapeutic gene, such that treating and ameliorating cardiovascular disease would be promoted, this being the intent of the claimed invention as per specification.

The specification is not enabling in its disclosure as it fails to teach the correlation between the expression of a lacZ, a reporter gene encoded by rAAV in mice for up to 8 weeks, and the expression of any therapeutic transgene encoded by rAAV to treat any cardiovascular or

ameliorate any cardiovascular condition in any and all mammalian species, especially humans. According to Crystal: humans are not simply large mice, in that there have been several surprise examples in which predictions from gene transfer studies in experimental animals have not been borne out in human safety and efficacy trials(Crystal, see page 410, left col, last para). Therefore, the expression of a reporter gene in mice is not predictive of the expression of a therapeutic transgene in the treatment of any cardiovascular disease in any mammal, especially humans.

4. The physiological art of treating a cardiovascular condition by infusing a rAAV vector into a coronary artery or sinus, encoding a therapeutically effective molecule which when expressed would be effective in treating or ameliorating any cardiovascular condition, in any mammal, especially humans, at the time of filing would have been considered unpredictable.

Anderson states that AAV vectors are used in clinical trials and it is the only known mammalian virus which shows preferential integration into a specific region in the genome. However, the present AAV vectors have several drawbacks in that they appear to integrate in a non-specific manner; some cells require very high multiplicity of infections; the AAV genome is small so only about 4.8 kb of DNA could be added; and the production of viral particles is still very labor intensive because efficient packaging cells have yet to be developed(Anderson, see page 28, right col, 1st para). Therefore, the method of the present invention, treating any cardiovascular condition by infusing rAAV into any coronary artery or coronary sinus, at the time of filing would have been unpredictable for the reasons cited above.

5. In the absence of specific guidance which is lacking in the specification as filed, and given the state of the art at the time of filing, coupled with the reasons discussed above, it would require undue experimentation for one skilled in the art to practice the methods or use the claimed products as disclosed in the specification.

It would require undue experimentation to determine which specific therapeutic molecule and how large, under which specific promoter, encoded by rAAV, administered by what route, and infused for what length of time, would be efficacious in the treatment or amelioration of which specific cardiovascular condition. This is considered trial and error experimentation to determine the innumerable parameters for successful gene delivery and treatment of any therapeutic molecule via rAAV, and as such, represents a mere invitation to experimentation.

Furthermore, it would require *de novo* experimentation to determine if lacZ expression in mice cardiomyocytes is generally correlative to the expression of any therapeutic gene in cardiomyocytes in any mammal, especially humans, and whether or not it would be predictive of success in treating and ameliorating cardiovascular disease.

Therefore, the specification, while being enabling for a method of transducing and expressing a reporter gene, lacZ in mice hearts, does not provide enablement for a method of treating any cardiovascular conditions in any animal.

The claims are free of the prior art. At the time of filing, the prior art did not teach nor suggest the method of treating cardiovascular conditions by the infusion of rAAV into a coronary artery or coronary sinus as claimed.

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yvette Connell, whose telephone number is 703-308-7942. The examiner can normally be reached on Monday-Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 703-308-0447.

Any inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Yvette Connell

July 31, 2000

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
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